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PRINCIPAL INVESTIGATOR: Jeffrey I. Joseph, D.O.

CONTRACTING ORGANIZATION: Thomas Jefferson University
Philadelphia PA 19107

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Jeffrey I. Joseph, D.O.

E-Mail: Jeffrey.Joseph@jefferson.edu

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14. ABSTRACT
This final report describes the data collected to evaluate the performance of two glucose sensor technologies (an interstitial fluid glucose sensor and a vascular glucose sensor) in perioperative surgical patients with diabetes. To date, all 10 patient studies specified in the statement of work have been completed. A description of the data and a formal description of the analyses to be preformed are presented herewith. All analyses will be completed in the next six months at which time an addendum to this report will be submitted.

15. SUBJECT TERMS
Continuous Glucose Monitoring (CGM), Glucose Sensor, Stress Hyperglycemia

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Introduction

The purpose of the research was to evaluate two glucose sensing technologies in the perioperative setting in diabetic patients and patients with stress hyperglycemia. The Medtronic MiniMed Telemetered Glucose Monitoring System (TGMS) and the Medtronic MiniMed Vascular Glucose Monitoring System (VGMS) were evaluated in 10 surgical patients. Prior to surgery, each subject will be brought into the hospital and one (1) VGMS, if available, and up to six (6) TGMS sensors were inserted. The VGMS was introduced through the central line catheter and advanced to the superior vena cava. The TGMS sensors were placed into the fatty tissue of the upper arm, upper thigh, and/or abdomen. Clinical management of the subject was the responsibility of the primary care-giver. The subject was monitored pre-, intra-, and postoperatively for a total of 60 hours of observation. Frequent arterial (every 20 minutes), venous (every 60 minutes), and capillary (every 3 hours) blood samples were obtained. All samples were assayed for glucose in duplicate. Arterial and venous blood was assayed for blood gases, electrolytes, lactate, insulin and fatty acids. A research nurse recorded changes in infusion rates of IV fluids, changes in body position, patient state (sedated, awake, sleeping, ambulating, etc.), procedure state (pre-op, surgery, post-op), meals (time, duration, size and content), and medications (time, type and dose). This clinical information and blood chemistry data are being used to understand the clinical conditions that occur during nominal sensor function, dysfunction, and failure. Reference blood glucose and sensor data are being used to investigate recalibration requirements for the VGMS and TGMS to achieve a given measurement accuracy. In addition, methods to improve measurement accuracy using multiple sensors are being explored using the reference blood glucose and TGMS sensor data.

Body

The primary objective of this project is to evaluate two types of continuous glucose sensors in ten (10) surgical patients. The project start date was 02/01/04 with an initial end date of 01/31/05. The time expended securing regulatory approvals and the limited availability of the VGMS sensors prompted the Principal Investigator to seek several time extensions (please see the 2006 Annual Report for specific details regarding these delays). Ultimately, the final end date for the project was 01/31/07. A summary of the key regulatory and scientific events in this project is given in Table 1 and a description of protocol modifications is given in Table 2.

The ten patient studies specified in the statement of work have been completed. When regulatory approvals were in place and investigational devices were on hand, we averaged two patient studies per month. Initially, it took over a year to secure regulatory approval and prepare for data collection. An additional delay was encountered while the VGMS sensors were resterilized. The gap between the first and second patient studies was the result of the lengthy resterilization process for the VGMS sensors. The gap between the fifth and sixth patient studies was the result of the time required to seek sponsor and regulatory approval to continue the research without VGMS sensors.

Data analysis is ongoing. The last patient studied concluded on 01/19/07, making it impossible to complete the data analysis prior to submission of this report. Preliminary results are reported, incomplete analyses are identified and their projected dates of completion are defined herewith.

Table 1: Project Timeline

Date	Event
06/10/03	Submitted research proposal
09/30/03	Received award letter
01/22/04	Received award contract
03/19/04	Initial investigational device exemption (IDE) submission to FDA
08/16/04	IDE granted
12/28/04	IRB approval
01/07/05	HSRRB approval
03/04/05	Annual progress report to IRB (submitted to FDA and HSRRB on 04/04/05)
03/15/05	Medtronic visit for investigational device delivery and training (received 5 VGMS sensors)
03/29/05	Amendment 1 submission to IRB
04/08/05	OMNI 9 (reference device) installed and qualified
04/11/05	IRB approval of Amendment 1
04/12/05	expired VGMS sensors returned to Medtronic for resterilization
04/25/05	HSRRB approval of Amendment 1
05/24/05	FDA acceptance of Amendment 1
06/15/05	6-month no-cost time extension request submitted to Sponsor
07/22/05	Sponsor approves time extension (new end date: January 31, 2006)
09/25/05	Amendment 2 submission to IRB
10/28/05	HSRRB approval of Amendment 2
11/04/05	IRB approval of Amendment 2 (initially approved on 10/13/05 but a minor revision to the consent form required a new approval letter)
11/23/05	FDA acceptance of Amendment 2

11/23/05	Received shipment of 10 resterilized VGMS sensors (Serial No. S09174, S09175, S09177, S09178, S09179, S09183, S09184, S09186, S09193, S09200)
12/05/05	**First patient study (Subject A2)**
12/08/05	12-month no-cost extension request submitted to Sponsor
12/15/05	Returned used VGMS sensors to Medtronic (Serial No. S09174)
01/07/06	Sponsor approves time extension (new end date: January 31, 2007)
01/15/06	9 remaining VGMS sensors sterile shelf-life expired (11/23/05 shipment)
02/08/06	2006 Annual Report to Sponsor
02/17/06	Amendment 3 submitted to IRB
02/20/06	expired VGMS sensors returned to Medtronic for resterilization (Serial No. S09175, S09177, S09178, S09179, S09183, S09184, S09186, S09193, S09200)
03/06/06	IRB acceptance of Amendment 3
03/14/06	Medtronic letter describing limited availability of VGMS sensors
03/30/06	Sponsor approved revised Statement of Work
05/19/06	Received shipment of 4 resterilized VGMS sensors (Serial No. S09177, S09183, S09184, S09193)
05/19/06	Received shipment of 20 sterile TGMS sensors (Lot D206)
05/22/06	Amendment 3 submitted to HSRRB
05/23/06	HSRRB acceptance of Amendment 3
05/31/06	Amendment 3 submitted to FDA
06/07/06	**Second patient study (Subject B2)**
06/08/06	Two (2) abstracts accepted by American Society of Anesthesiology (ASA)
06/13/06	Returned used VGMS sensors to Medtronic (Serial No. S09184)
06/16/06	**Third patient study (Subject A3)**
06/23/06	**Fourth patient study (Subject B3)**
06/26/06	Received 6 sterile TGMS sensors (Lot E126)
06/27/06	**Fifth patient study (Subject C2)**
06/27/06	Received shipment of 20 sterile TGMS sensors (Lot E246)
07/06/06	Returned three (3) used VGMS sensors to Medtronic (Serial No. S09177, S09183, S09193)
07/13/06	Amendment 4 submitted to IRB
07/14/04	Annual progress report submitted to FDA
07/28/06	FDA acceptance of Amendment 3
07/31/06	IRB acceptance of Amendment 4
07/31/06	Amendment 4 submitted to HSRRB
08/16/06	HSRRB acceptance of Amendment 4
08/22/06	Amendment 4 submitted to FDA
09/18/06	FDA acceptance of Amendment 4
10/14/06	Presented preliminary data at the 2006 ASA Conference in Chicago, IL
11/08/06	**Sixth patient study (Subject C3)**
11/09/06	Received shipment of 10 sterile TGMS sensors (Lot J236)
11/14/06	**Seventh patient study (Subject D3)**
12/13/06	**Eighth patient study (Subject E3)**
12/20/06	Received shipment of 10 sterile TGMS sensors (Lot K226)
01/10/07	**Ninth patient study (Subject F3)**
01/17/07	**Tenth patient study (Subject D2)**
01/17/07	Received shipment of 10 sterile TGMS sensors (Lot L156)

Table 2: Amendment Summary

Amendment	Description
4	1. Documents have been modified to remove references to the VGMS sensor. The consent form has been modified with the words (TGMS Only) in the Medical Title. The study will be completed using the TGMS sensor only. 2. The protocol has been modified to decrease the amount of time blood will be sampled from the radial artery catheter, from 60 hours to a maximum of 36 hours. Sampling blood every 20 minutes from the radial artery catheter has inconvenienced the study subjects, especially the second night of sampling. Inconvenience due to radial artery catheter sampling has caused two patients to discontinue the study prematurely. 3. Drs. Charles Yeo and Zvi Grunwald where added as co-investigators.
3	1. The algorithms to management blood glucose levels with intravenous or subcutaneous insulin have been removed from the protocol (Thomas Jefferson University Hospital currently has standardized clinical protocols for the management of blood glucose levels in patients that are managed in the Surgical Intensive Care Unit, Intermediate Surgical Intensive Care Unit, and general surgical floor). 2. Non-diabetic patients scheduled to undergo pancreatic surgery are included as eligible subjects. 3. Preoperative data collection period was changed from 4-12 hours to 1-12 hours.
2	1. Eligibility requirement that type 2 diabetic subjects must use insulin in the outpatient setting to manage their glucose levels was removed. 2. Although twelve diabetic subjects will be enrolled, there may not be an equal division between type 1 and type 2 diabetic subjects.
1	1. Same-day admissions patients (patients arrive to the hospital and getting admitting on the day of their surgery) are included as eligible subjects. 2. Preoperative data collection time was changed from 12 hours to 4-12 hours
*	1. The reference instruments that were chosen to measure blood gases, electrolytes and metabolites including glucose (i.e., i-STAT and HemoCue B-Glucose analyzer) were replaced with one point-of-care instrument, OMNI 9 (Roche Diagnostics). 2. Venous blood samples will be obtained from the central venous line instead of the antecubital venous catheter. 3. The follow-up procedure was changed to allow for further future contact to assess subject's general health and reaction to IV and ISF sensors. 4. Potential subjects with thrombocytopenia and subjects with an implanted pacemaker, defibrillator, or a pulmonary artery catheter are ineligible. 5. Sites of VGMS and TGMS insertion will be photographed.

* Changes to the protocol and consent forms were made at the insistence of the IRB and FDA (after the IDE was granted). The FDA was notified of these changes in a supplement to the original application.

The original tasks set forth in the statement of work for this research project are given in Table 3 (modifications to the statement of work appear in italics).

Table 3: Statement of Work

Task	Description
1	Arrays of needle-type glucose sensors will be developed for the real-time monitoring of ISF glucose levels in hospitalized patients with type 1 and type 2 diabetes. ISF glucose sensors will be modified in collaboration with Medtronic-MiniMed scientists to provide continuous monitoring of the six output signals. Two 3-sensor arrays will be combined (sensor hardware, cables, software, portable PC) to provide real-time recording and display of six simultaneous sensor output signals. Custom software will be developed to record detailed clinical/chemistry data in real-time at the bedside. *The eligible patient population was broadened to include non-diabetic patients undergoing a pancreatectomy.*
2	A human clinical study will be performed to investigate the correlation between sensor output and blood glucose levels in hospitalized patients with type 1 (n= 5) and type 2 (n=5) diabetes. Sensor arrays will be inserted into the subcutaneous tissue of the abdomen (3-sensor array) and upper arm (3-sensor array) prior to anesthesia and surgery. Six sensor output signals will be recorded over a 60-hour pre-op, intra-op, and post-operative period. Sensor signals will be compared to reference blood glucose measurements simultaneously sampled from arterial, capillary, and venous blood (every 20 to 60 minutes). Detailed clinical and blood/urine chemistry data will be entered into a PC database by a bedside vigilant observer. *The eligible patient population was broadened to include non-diabetic patients undergoing a pancreatectomy. The subpopulation sample sizes (i.e., 5 patients with type 1 diabetes and 5 patients with type 2 diabetes) were removed. The chest and thigh were added as sites for sensor insertion. The frequency of arterial blood sampling was every 20 minutes for 36 hours, the frequency of venous blood sampling was every 60 minutes (which coincided with every third arterial sample) for 60 hours, and the frequency of capillary blood sampling was every 3 hours (which coincided with every third venous sample) for 60 hours. Clinical and blood/urine chemistry data was recorded long-hand at the bedside and transcribed into a electronic spreadsheet after the conclusion of the study.*
3	The above data set will be studied to determine the effects of averaging, smoothing, and correlating multiple (6) ISF sensor output signals on the accuracy, precision, robustness, and noise of the sensor array as a possible input to the artificial pancreas (AP) computer controller. The accuracy of ISF sensor glucose measurements will be evaluated as a function of the number of simultaneously measured ISF sensor outputs signals. The correlation after fault-analysis of one or more sensors within a two- to six-sensor array will be investigated.
4	The above data set will be studied to determine the optimal frequency and timing of sensor re-calibration in the hospital setting. The time-dependent behavior of the ISF sensors will be modeled. Modeling ISF sensor array behavior may allow us to predict sensor drift and make automatic adjusts in the calibration coefficient, in order to decrease the need for frequent reference blood samples. We plan to determine the relationship between sensor accuracy and frequency of re-calibration, based upon a retrospective analysis of ISF glucose sensor data and reference blood glucose (BG) data. We also plan to determine how the timing of sensor recalibration (during a period of glucose level stability versus a period of instability) affects sensor array accuracy in relation to reference BG measurements. Fault prediction methods will be developed to permit the identification (and subsequent removal) of an individual ISF sensor signal from a sensor array that does not follow the defined behavior of a stable and nominal sensor.
5	The detailed database of clinical information (vital signs, inputs & outputs, timing of medications, fluids, procedures, and meals) and blood chemistry data, (blood glucose, lactate, pH, PaCO2, PaO2, SaO2, fatty acids, insulin, electrolytes, BUN, hematocrit) will be studied to understand the clinical conditions that occur during nominal sensor function, dysfunction, and failure. This database will be used in the future by Jefferson, Drexel, and Medtronic-MiniMed scientists to develop a robust computer control algorithm for the in-hospital AP system.

In regards to **Task 1**, Medtronic provided equipment and on-site instruction for both investigational devices (TGMS and VGMS) on 03/15/2005.

- The VGMS consisted of an intravascular glucose sensor lead assembly, an extension lead, and a transceiver, which houses the battery and electronics (Figure 1). The transceiver was originally developed as a long-term implantable glucose monitor. For the current study, however, the transceiver was worn external to the patient. The hand-held Personal Programming Communicator (PPC) was used to communicate wirelessly with the transceiver, allowing us to port the glucose sensor data to a personal computer for storage and display using custom software (Clinician Station) developed by Medtronic.

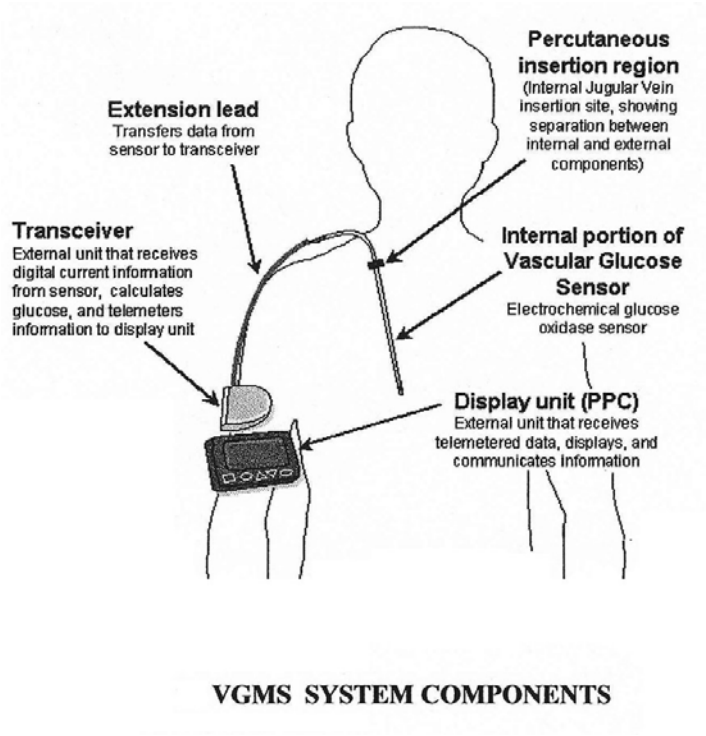


Figure 1: Diagram of VGMS including the vascular glucose sensor, extension lead, transceiver, and personal programming communicator (PPC).

- The TGMS consisted of a sensor, transmitter, transceiver, and laptop computer (Figure 2). Each sensor was connected to a transmitter via a short cable. The transmitter communicated to a nearby transceiver. The transceiver was connected to the serial port of a laptop computer which displayed and stored the received data. By staggering (in time) the transmission of multiple sensor/transmitter units, it was possible to record the data of six sensors simultaneously on one computer using custom software (ControlTool) developed by Medtronic.

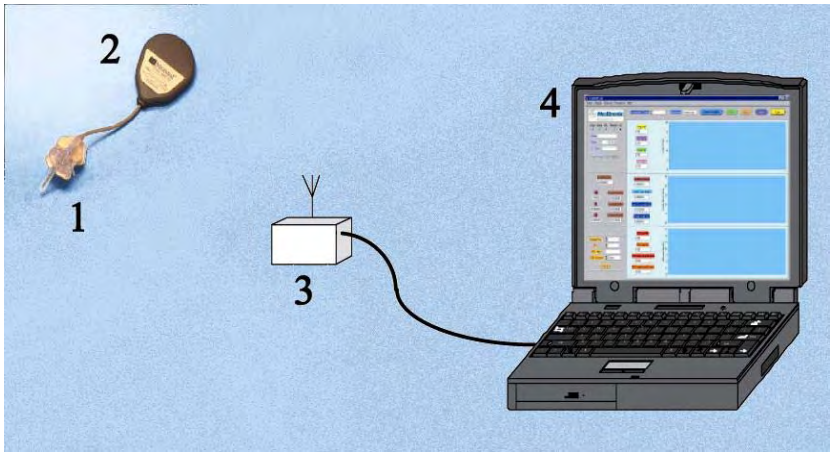


Figure 2: Diagram of the TGMS including (1) ISF sensor, (2) transmitter, (3) transceiver and (4) portable computer.

During the course of data collection, TJU investigators, supported by Medtronic engineers, spent considerable time diagnosing a problem that caused large block of TGMS sensor data to be lost in patient studies B3 and C2. Benchtop testing was performed in an attempt to recreate the problem. The final conclusion was that the problem was caused by the laptop computer. A replacement laptop computer was used for patient studies C3, D3, E3, F3, and D2.

In regards to **Task 2**, we completed the ten patient studies specified in the statement of work. Out of the ten subjects studied, four subjects (A2, B2, C2 and D2) had a prior diagnosis of type 2 diabetes. The remaining six subjects (A3, B3, C3, D3, E3 and F3) were undergoing a pancreatic resection procedure but did not have diabetes. We were unable to recruit any subjects with type 1 diabetes. The sex, date of birth, age, height, weight, C-peptide level and HbA1c for each subject is given in Table 4.

Table 4: Subject Demographics

	Subject ID	**Sex**	**DOB**	**Age** years	**Height** inches	**Weight** pounds	**C-Peptide*** ng/ml	**HbA1c†** %
1	A2	F	02/22/52	53	62	252	1.9#	7.3
2	B2	M	08/19/32	73	74	246	0.9	6.5
3	A3	F	03/27/59	47	64	111	0.7	6.1
4	B3	M	09/04/50	55	70	158	0.8	5.3
5	C2	M	10/29/37	68	69	151	1.3	7.5
6	C3	M	07/09/48	58	72	169	2.1	6.1
7	D3	M	01/29/47	59	74	230	1.0	5.6
8	E3	F	03/30/55	51	62	113	1.2	5.5
9	F3	M	10/01/50	56	72	205	0.8	5.0‡
10	D2	M	12/30/43	63	73	276	2.9	5.6‡

* reported normal range is 0.8-3.5 ng/ml unless otherwise noted
\# reported normal range is 0.8-3.1ng/ml
† reported normal range is 3.6-6.9% unless otherwise noted
‡ reported normal range is 4-6%

The first five subjects (A2, B2, A3, B3, and C2) received both types of glucose sensors (TGMS and VGMS). The remaining five subjects (C3, D3, E3, F3, and D2) were studied with the TGMS sensor only (no VGMS sensors were available during their periods of study). The study dates and duration for each subject are given in Table 5. The *start time* and *end time* are when the first and last reference blood samples were obtained. Subjects B2, B3, and C2 were not studied for 60 hours. The study of subject B2 was discontinued when the arterial catheter failed after 43 hours (the venous line failed after 12 hours). Subjects B3 and C2 requested to withdraw from the study after 35 and 32 hours, respectively. These two subjects and their families were noticeably upset regarding diagnosis of unresectable cancer of the pancreas.

Table 5: Data Collection Summary

	Subject ID	**Data Collection**		
		Start Time	*End Time*	*Duration (hrs)*
1	A2	12/05/2005 10:55	12/07/2005 21:25	58.5
2	B2	06/07/2006 11:04	06/09/2006 06:37	43.6
3	A3	06/16/2006 07:50	06/18/2006 19:46	59.9
4	B3	06/23/2006 07:40	06/24/2006 19:20	35.7
5	C2	06/27/2006 07:25	06/28/2006 16:00	32.6
6	C3	11/08/2006 08:42	11/10/2006 20:04	59.4
7	D3	11/14/2006 08:20	11/16/2006 20:03	59.7
8	E3	12/13/2006 07:14	12/15/2006 20:05	60.9
9	F3	01/10/2007 08:00	01/12/2007 19:48	59.8
10	D2	01/17/2007 08:07	01/19/2007 20:09	60.0

All data collected in the course of the project have been placed in electronic spreadsheets (Microsoft Excel). Each patient study has its own spreadsheet with the following worksheets: Patient, Assessments, Reference Data, AccuChek, OMNI9, VGMS, and TGMS. The data stored in each worksheet is described in Table 6. All reference data from the Roche Diagnostic OMNI 9 (pH, pO_2, pCO_2, Na^+, K^+, Cl^-, iCa^{++}, ctHb, HHb, O2Hb, COHb, MetHb, SulfHb, Hct, Lac, and Glu) was stored electronically with a printed paper backup. Data were exported into a tab-delimited ASCII text file. Clinician Station stored VGMS sensor data in a comma-delimited ASCII text file. ControlTool stored TGMS sensor data in tab-delimited ASCII text files. The OMNI 9, ControlTool and Clinician Station files have been retained unaltered. All other data was recorded on paper forms by hand and transcribed into the spreadsheets. All data collection forms have been retained. Each patient study has its own data collection binder that contains these forms.

Table 6: Description of Patient Data in Electronic Spreadsheet

Worksheet	**Data**
Patient	A brief description of the patient. Data includes the history of the present illness (HPI), past medical history (PMSH), social history (SH), family history (FH), medication list (Meds), height, weight, blood pressure, pulse rate (PE) and procedure
Assessments	Time stamped record of patient vital signs (Temp, HR, Rhythm, BP, MAP, RR), skin temperature (temperature probes placed at each of the two arrays of subcutaneous glucose sensors), activity, sedation, pain, meals, intravenous fluids, medications, and other observations (e.g., position during surgery, moved from the ICU to general floor, notified primary care nurse of pending hypoglycemia, change in IV insulin infusion rate,

	medications, lab results, etc.).
Reference Data	A clean organized presentation of the OMNI 9 data
AccuChek	The time-stamped results of Accu-Chek measurements of capillary, venous and arterial blood glucose.
Urine	Hourly measurements of urine volume, color, specific gravity (SG), and pH as well as measurements for leukocytes, nitrate, protein, glucose, ketones, urobilin, bilirubin, and blood in the urine when a Foley catheter was in place.
OMNI9	The data from the OMNI 9 which has been reviewed to correct user input errors and remove outliers. Any changes that have been made to these data have been tracked with comments from the reviewer.
VGMS	VGMS sensor data which includes Date and Time, Isig Glu (output from glucose-oxidase coated electrode), Isig Oxy (output from bare electrode), Sensor O2 (O2 data using in-vitro calibration), Sensor C6 (glucose data using in-vitro calibration), Ori Time (encoded diagnostic and performance data), Date and Time, Temperature (Celius) from the VGMS (core temperature data decoded from Ori Time)
TGMS	TGMS sensor data which includes the time and sensor output for each of the six TGMS sensors.

For each subject, a VGMS sensor (if available) was inserted into the superior vena cava through an 8.5 french Cordis placed in right jugular vein. For each subject, six TGMS sensors were inserted into the upper arm, upper chest, or thigh region by the principal investigator. Table 7 lists the location of each TGMS sensor by subject. Sensors 1-3 comprise the first array and sensors 4-6 comprise the second array. In total, 6 sensors were placed in the arm, 36 sensors were placed in the chest and 18 sensors were placed in the thigh. The choice of sensor location was based on an assessment of the subcutaneous tissue mass. In all subjects, the surgical procedure prevented sensors from being placed in the abdomen. A photograph of the both investigational devices *in situ* is given in Figure 3.

Table 7: TGMS Sensor Location

Sensor	Subject A2	Subject B2	Subject A3	Subject B3	Subject C2
1	medial right chest	upper right chest	upper left chest	upper right chest	upper right chest
2	right chest	middle right chest	middle left chest	middle right chest	middle right chest
3	lateral right chest	lower right chest	lower left chest	lower right chest	lower right chest
4	upper right upper arm	middle right upper arm	upper right chest	upper left chest	middle left chest
5	middle right upper arm	upper right upper arm	middle right chest	middle left chest	upper left chest
6	lower right upper arm	lower right upper arm	lower right chest	lower left chest	lower left chest

Sensor	Subject C3	Subject D3	Subject E3	Subject F3	Subject D2
1	upper left chest	upper right chest	lateral left thigh	lateral left thigh	medial left thigh
2	middle left chest	middle right chest	left thigh	left thigh	left thigh
3	lower left chest	lower right chest	medial right thigh	medial left thigh	lateral left thigh
4	upper right chest	upper left chest	medial left thigh	lateral right thigh	medial right thigh
5	middle right chest	middle left chest	lateral right thigh	right thigh	right thigh
6	lower right chest	lower left chest	right thigh	medial right thigh	lateral right thigh

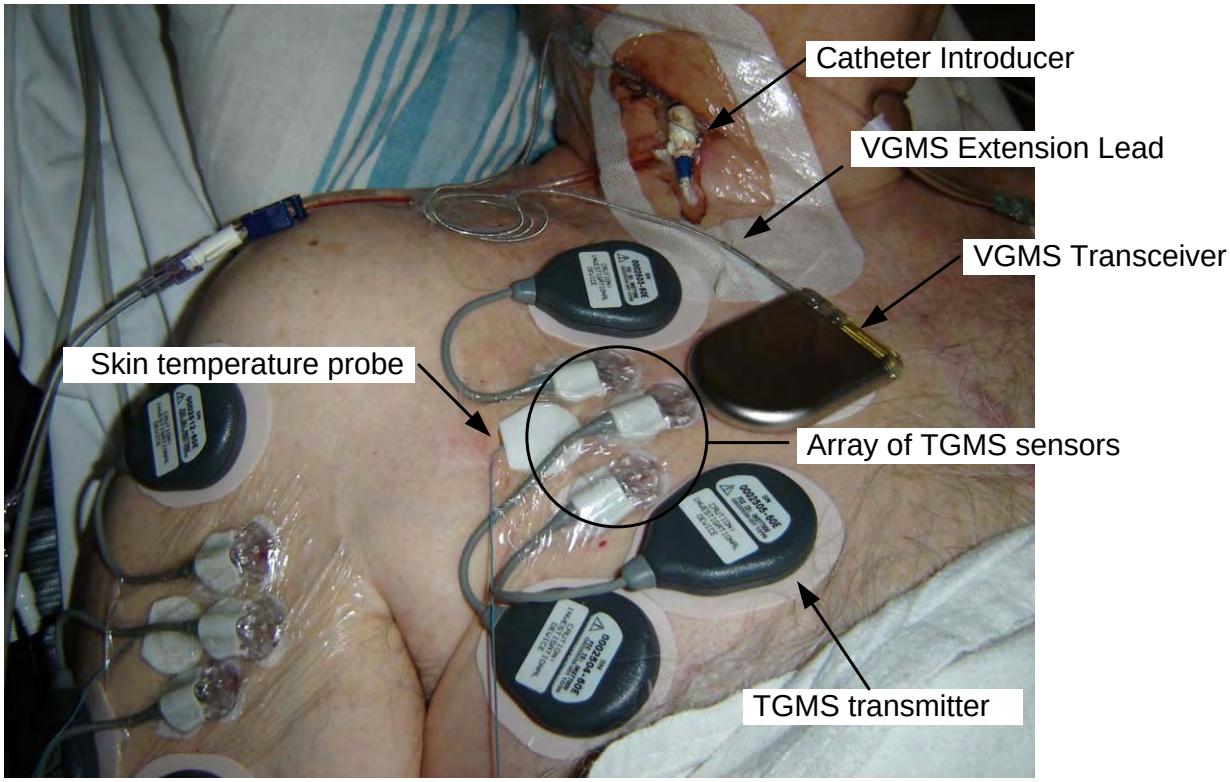


Figure 3: The investigational devices *in-situ* during a patient study

Catheters were placed in the radial artery and the jugular vein for reference blood sampling throughout the study. Arterial samples were obtained every 20 minutes and venous samples were obtained every hour (coinciding with every third arterial sample)[*]. Initially, arterial and venous samples were obtained over the entire study period. The protocol was revised after the first five studies to limit the arterial blood sampling to a maximum of 36 hours (studies C3, D3, E3, F3, and D2). Subjects reacted negatively to the frequency of sampling and degree of subject compliance required to obtain the arterial sample.

Table 8 contains the time period in which each reference sampling site was operational. We reach the maximal time limit for the radial artery sampling in only the last two studies (F3 and D2). It was not an insignificant task to keep arterial line operation throughout the study. In one of the 10 studies (B2), the venous catheter failed. In subjects B3 and C2, the venous sampling was limited because the subjects withdrew from the study.

[*] Reference capillary samples were obtained every three hours (coinciding with every third venous sample). The analysis of this data is not included within this report.

Table 8: Duration of Operation for Reference Blood Sampling Catheters

Subject	Duration (hours)	
	Radial Artery	*Jugular Vein*
A2	48.9	59.8
B2	45.7	12.8
A3	48.7	60.6
B3	32.5	34.5
C2	33.0	19.9
C3	30.0	59.8
D3	28.7	60.0
E3	19.8	59.8
F3	36.1	59.2
D2	35.9	57.2

Summary statistics for reference glucose measurements are given in Table 9. The number of samples used in the calculation of the minimum, maximum, and mean values of arterial and venous blood glucose were subjected to the following criteria: the sample was tested in duplicate and (2) the duplicate measurements differed by less than 10%[†]. This information is presented as box plots in Figure 4 and Figure 5 for the arterial and venous reference data, respectively. Please note that the reference glucose data from these two sites have different sampling frequencies and lengths so a direct comparison between them should not be made.

Table 9: Reference Blood Glucose Statistics

Subject	Arterial Glucose				Venous Glucose			
	samples (n)	*minimum (mg/dl)*	*maximum (mg/dl)*	*mean (mg/dl)*	*samples (n)*	*minimum (mg/dl)*	*maximum (mg/dl)*	*mean (mg/dl)*
A2	81	70	214	136	36	79	230	126
A3	119	81	189	122	58	55	149	107
B2	100	96	289	194	6	94	245	146
B3	82	110	199	149	29	102	177	135
C2	45	72	221	159	14	65	183	133
C3	59	107	212	145	46	88	184	137
D3	61	81	183	131	53	78	185	131
E3	48	104	181	145	48	105	181	126
F3	101	101	185	140	47	80	174	120
D2	102	77	239	136	53	72	269	155

[†] the formula for the percent difference in measurements is $2|x_1-x_2|/(x_1-x_2) < 0.1$ where x_1 is the first test and x_2 is the second test using the same blood sample.

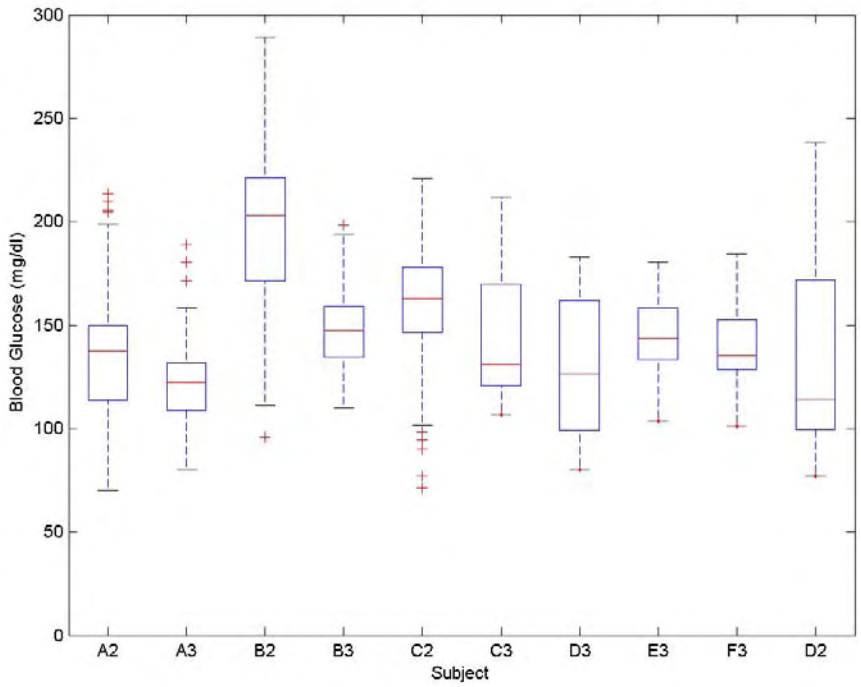


Figure 4: Reference arterial glucose box plot

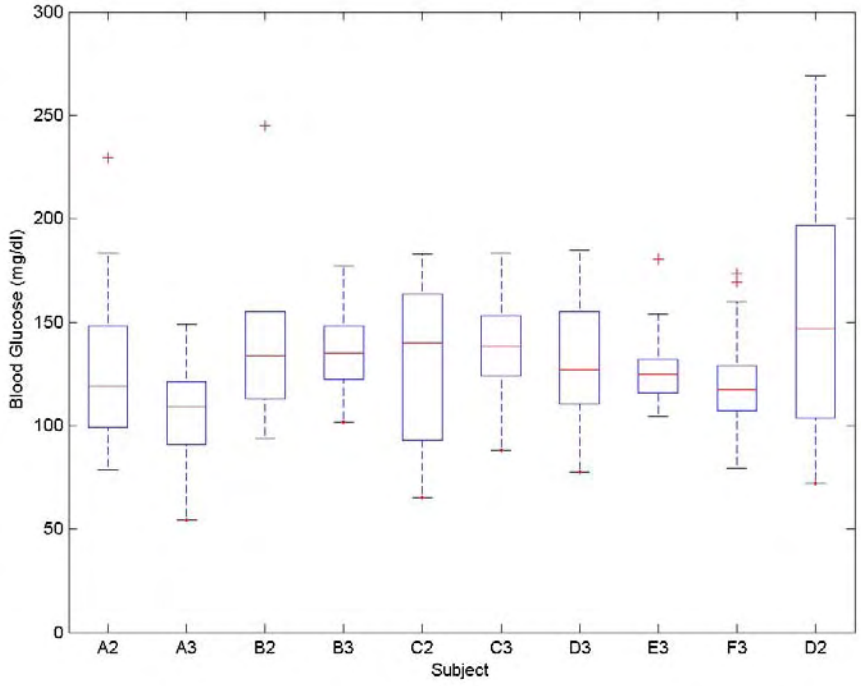


Figure 5: Reference venous glucose box plot

Plots of the reference blood glucose and glucose sensor data are provided in the Appendix. A three panel figure is provided for each subject (10 figures in total).

- Top Panel: reference arterial (red) and venous (blue) blood glucose measurements. An open circle indicates a sample was tested twice and the duplicate measurements differed by less than 10% (the formula for the percent difference in measurements is $2*|x_1-x_2|/(x_1-x_2) < 0.1$ where x_1 is the first test and x_2 is the second test using the same blood sample). An asterisk indicates that the sample was either not measured in duplicate or measured in duplicate with the duplicate measurements differing by 10% or more.
- Middle Panel: outputs from six TGMS sensors (blue traces are from one sensor array and red traces are from the second sensor array). TGMS Sensors 1, 2, and 3 are dark blue, blue and light blue, respectively. TGMS Sensors 4, 5, and 6 are dark red, red and light red, respectively.
- Bottom Panel: in-vitro calibrated VGMS sensor data.

In the first study (subject A2), reference data could not be tested (and hence was not collected) for one period of time (approximately 4 hours in duration) due to problems with the reference measurement device (OMNI 9). This problem was identified and precautions were put in place so it did not occur again. In addition, TGMS sensor data could not be collected for two brief periods of time due to technical issues with the computer's power supply. No overt sensors failures occurred during this study.

In the second study (subject B2), reference venous data was limited to less than 13 hours because of a failure of the sampling catheter. Since the VGMS sensor passed through the lumen of the catheter, a decision was made not to replace the catheter. The overt failure of TGMS sensor 1 can be observed after 20 hours of operation.

In the third study (subject A3), an overt failure of the VGMS sensor is seen after 36 hours of operation.

In the fourth study (subject B3), the subject withdrew after 35 hours of observation. Several periods of lost TGMS data occurred (the cause of this data lost was discussed previously in this report).

In the fifth study (subject C2), the subject withdrew after 32 hours of observation. One period of lost TGMS data occurred (the cause of this data lost was discussed previously in this report). Every TGMS sensor in the first array (sensors 1-3) failed during observation. The subject was extremely lean. TGMS sensors were placed in the left (first sensor array) and right (second sensor array) chest. When the sensors were removed, it was noted that all the sensors that had failed were no longer implanted in the subcutaneous tissue. The repeated arm motion of the subject had caused the sensor tips to unseat themselves. Once the tip of the sensor was no long in the subcutaneous tissue, the sensor's current output failed to track blood glucose levels.

In the sixth study (subject C3), the arterial catheter failed after 30 hours. No VGMS sensor was available for this and subsequent studies.

In the seventh study (subject D3), the arterial catheter failed after 28 hours. There was an overt failure of TGMS sensor 1. All TGMS sensors in the first array (right chest) experienced a spike in their outputs between hours 8 and 16. The 8^{th} hour of observation corresponds to the period when the surgical procedure was complete. The patient was moved off the surgical table onto a transport gurney, transported to the SICU (Surgical Intensive Care Unit), and moved off the

gurney to a bed. In addition, upon arrival in the SICU, a patient is bathed. It is possible that the sensors could have shifted during this time. Upon removal, it was noted that TGMS sensor 1 was no longer implanted.

In the eighth study (subject E3), the arterial catheter failed after 19 hours. A large block of lost TGMS data (approximately 5 hours) is due to a loss in power to the TGMS laptop. There is a very subtle change in reference venous blood glucose levels through the 60 hours of observation. In contrast, all TGMS sensors display a significant amount of noise.

In the ninth study (subject F3), both the arterial and venous catheter remained operational to the limit of their use. Intermittent spiking is observed in the outputs of TGMS sensors 1-3 (first array, left thigh).

In the last study (subject D2), both the arterial and venous catheter remained operational to the limit of their use. Overt failures of TGMS sensors 2 and 3 occurred early in the study whereas TGMS sensors 4 and 5 failed in the latter portion of the study.

Every TGMS sensor was photographed after explantation under magnification (Figure 6). The amount of blood at the site and on the sensor tip was assessed and recorded (Table 10). Every instance of an overt TGMS sensor failure corresponds to a dislodged sensor.

Table 10: TGMS Sensor Explantantion Notes

Sensor		Subject A2	Subject B2	Subject A3	Subject B3	Subject C2
1	sensor tip	clean	clean	clean	slight heme	n/a
	sensor base	slight heme	clean	slight heme	slight heme	n/a
	adhesion	good	good	good	good	none[1]
2	sensor tip	clean	moderate heme	clean	clean	n/a
	sensor base	clean	moderate heme	slight heme	clean	n/a
	adhesion	good	good	good	good	none[1]
3	sensor tip	clean	clean	clean	clean	n/a
	sensor base	clean	clean	clean	clean	n/a
	adhesion	good	good	good	good	none[1]
4	sensor tip	clean	clean	clean	clean	clean
	sensor base	clean	slight heme	clean	clean	clean
	adhesion	good	good	good	good	poor[2]
5	sensor tip	clean	significant heme	clean	significant heme[3]	clean
	sensor base	clean	significant heme	clean	significant heme	clean
	adhesion	good	good	good	good	good
6	sensor tip	clean	moderate heme	slight heme[3]	slight heme[3]	clean
	sensor base	clean	moderate heme	slight heme	slight heme	clean
	adhesion	good	good	good	good	poor[2]

Sensor		Subject C3	Subject D3	Subject E3	Subject F3	Subject D2
1	sensor tip	clean	n/a	slight heme	clean	moderate heme
	sensor base	clean	n/a	moderate heme	clean	moderate heme
	adhesion	good	none[1]	good	good	fair
2	sensor tip	clean	clean	slight heme	significant heme[3]	moderate heme
	sensor base	clean	clean	moderate heme	significant heme	moderate heme
	adhesion	good	good	good	fair	none[1]
3	sensor tip	clean	slight heme[3]	clean	slight heme	moderate heme
	sensor base	clean	slight heme	slight heme	slight heme	moderate heme
	adhesion	good	good	good	fair	none[1]
4	sensor tip	slight heme	clean	slight heme	slight heme	moderate heme
	sensor base	slight heme	clean	moderate heme	slight heme	moderate heme
	adhesion	good	good	good	fair	good
5	sensor tip	clean	clean	clean	clean	moderate heme
	sensor base	clean	clean	slight heme	clean	moderate heme
	adhesion	good	good	good	good	good
6	sensor tip	clean	clean	slight heme	clean	clean
	sensor base	clean	clean	moderate heme	clean	clean
	adhesion	good	good	good	good	good

1: sensor completely dislodged
2: sensor partially dislodged
3: active bleeding upon sensor removal

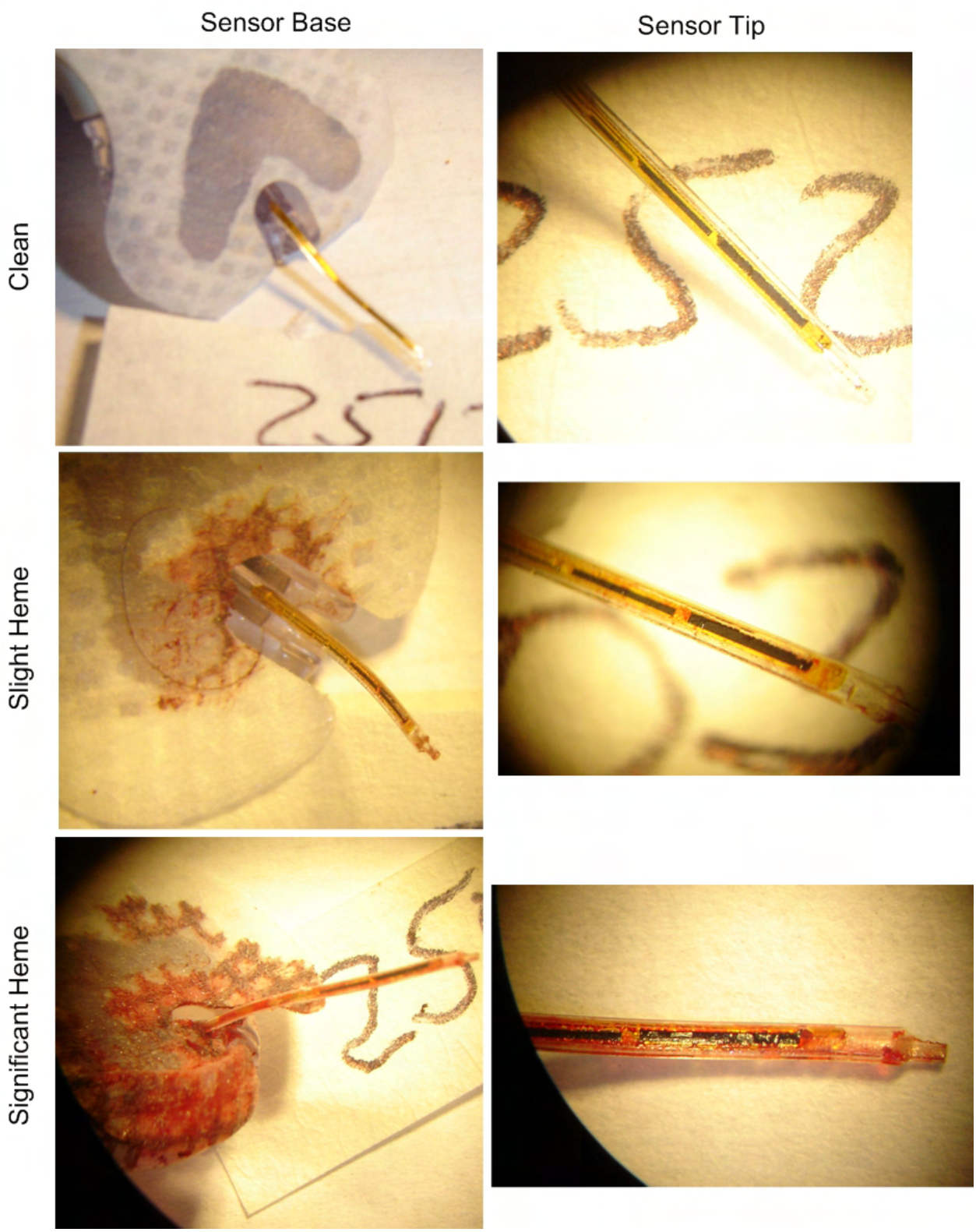


Figure 6: Photographs of explanted TGMS sensors

Work is ongoing to address **tasks 3-5** in Table 3. Data collection ended 01/19/07. There has not been sufficient time to complete all analyses. We have prepared a formal description of the analyses (see appendix). We expect to complete all analyses in the next six months at which time we will submit an addendum to this report.

Key Research Accomplishments

- Completed 10 patient studies
    - 5 studies with both VGMS and TGMS sensors
    - 5 studies with the TGMS sensors only
- Presented two abstracts at the 2006 ASA conference in Chicago, IL

Reportable Outcomes

Two abstracts analyzing the data from the first subject (patient A2) were accepted and scheduled for a poster discussion presentation at the 2006 Annual Meeting of the American Society of Anesthesiologists. The abstracts, entitled "Continuous Glucose Monitoring in the Perioperative Period" and "Lag Associated with Interstitial Glucose Sensors used in a Diabetic Surgical Patient", are included in the appendix.

Several manuscripts are in preparation.

Conclusions

Data analysis is ongoing. A future addendum to this report will contain the final conclusion to this research.

Preliminary analysis showed a high percentage of TGMS sensors that failed during the period of observation because the sensors did not remain within the subcutaneous space. In the outpatient setting, the abdomen is the preferred site for implantation for sensors like the TGMS sensor. The choice of the most appropriate placement for these sensors in the inpatient setting may not be a trivial task. If adequate subcutaneous tissue is present in the arm, this may be the most appropriate site for sensor placement.

References

No references included in this report.

Appendices

1. Reference Blood Glucose and Glucose Sensor Data: a three panel figure for each subject is provided (10 figures in total). Top Panel: reference arterial (red) and venous (blue) blood glucose measurements (an open circle indicates a sample was tested twice and the duplicate measurements differed by less than 10%; an asterisk indicates that the sample was either not measure in duplicate or measured in duplicate and the duplicate measurements differed by 10% or more). Middle Panel: outputs from six TGMS sensors (blue traces are from one sensor array and red traces are from the second sensor array). TGMS Sensors 1, 2, and 3 are dark blue, blue and light blue, respectively. TGMS Sensors 4, 5, and 6 are dark red, red and light red, respectively. Bottom Panel: in-vitro calibrated VGMS sensor data.
2. Data Analysis Plan
3. 2006 ASA Abstracts
    a. Hipszer B, Furlong KJ, Lessin JB, Grunwald Z, Joseph JI. Continuous Glucose Monitoring in the Perioperative Period. Abstract, ASA Annual Meeting of the American Society of Anesthesiology, October 2006, Chicago, IL.
    b. Hipszer B, Joseph JI. Lag Associated with Interstitial Glucose Sensors used in a Diabetic Surgical Patient. Abstract, Annual Meeting of the American Society of Anesthesiology, October 2006, Chicago, IL.
4. Research Personnel List

Appendix 1: Reference Blood Glucose and Glucose Sensor Data

Figure Description

- Top Panel: reference arterial (red) and venous (blue) blood glucose measurements. An open circle indicates a sample was tested twice and the duplicate measurements differed by less than 10% (the formula for the percent difference in measurements is $2*|x_1-x_2|/(x_1-x_2) < 0.1$ where x_1 is the first test and x_2 is the second test using the same sample). An asterisk indicates that the sample was either not measured in duplicate or measured in duplicate with the duplicate measurements differing by 10% or more.
- Middle Panel: outputs from six TGMS sensors (blue traces are from one sensor array and red traces are from the second sensor array). TGMS Sensors 1, 2, and 3 are dark blue, blue and light blue, respectively. TGMS Sensors 4, 5, and 6 are dark red, red and light red, respectively.
- Bottom Panel: in-vitro calibrated VGMS sensor data

Patient A2

Plasma Glucose (mg/dl)

TGMS Sensor (nA)

VGMS Sensor (mg/dl)

Time (hr)

Patient B2

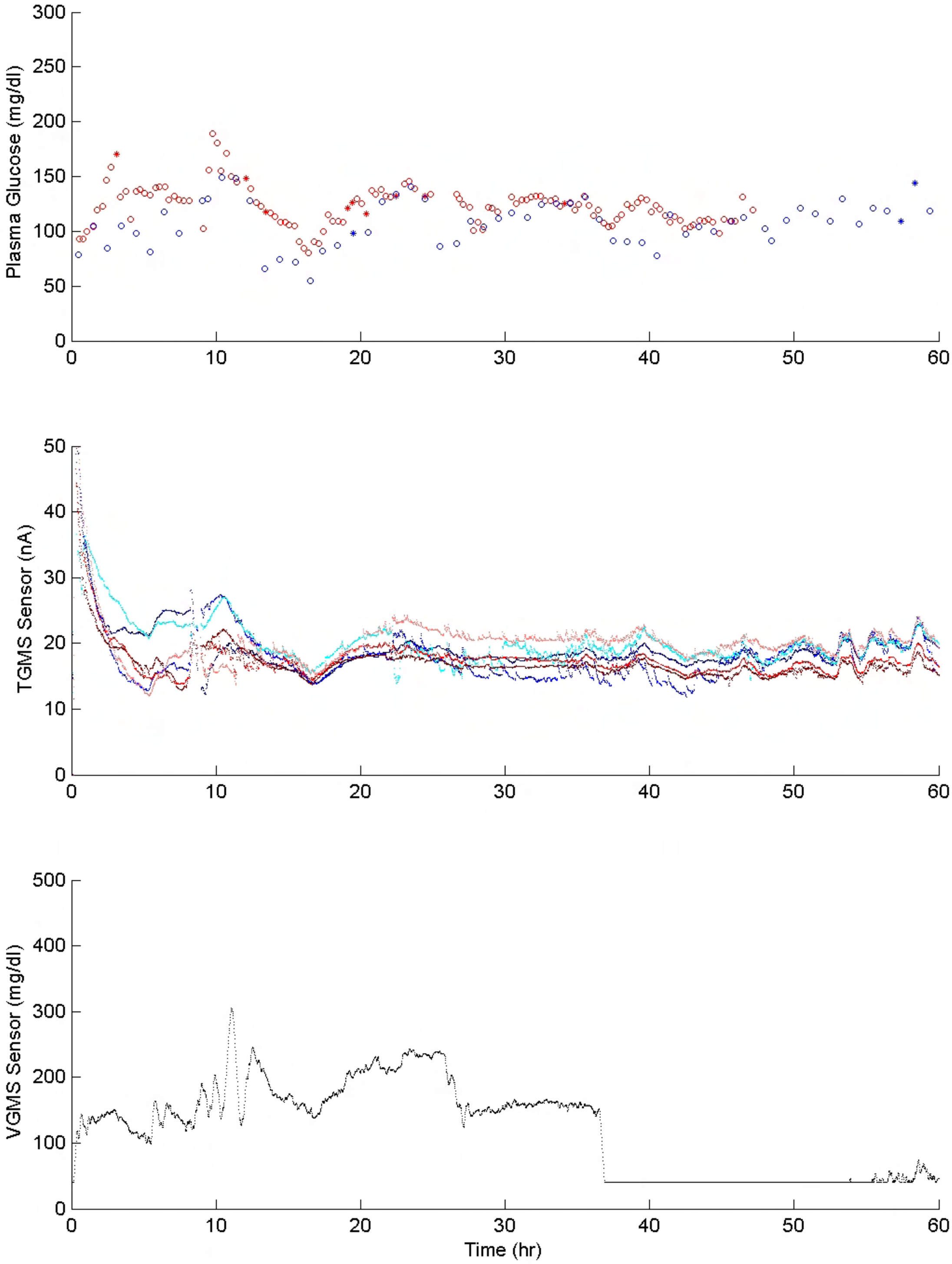
Plasma Glucose (mg/dl)

TGMS Sensor (nA)

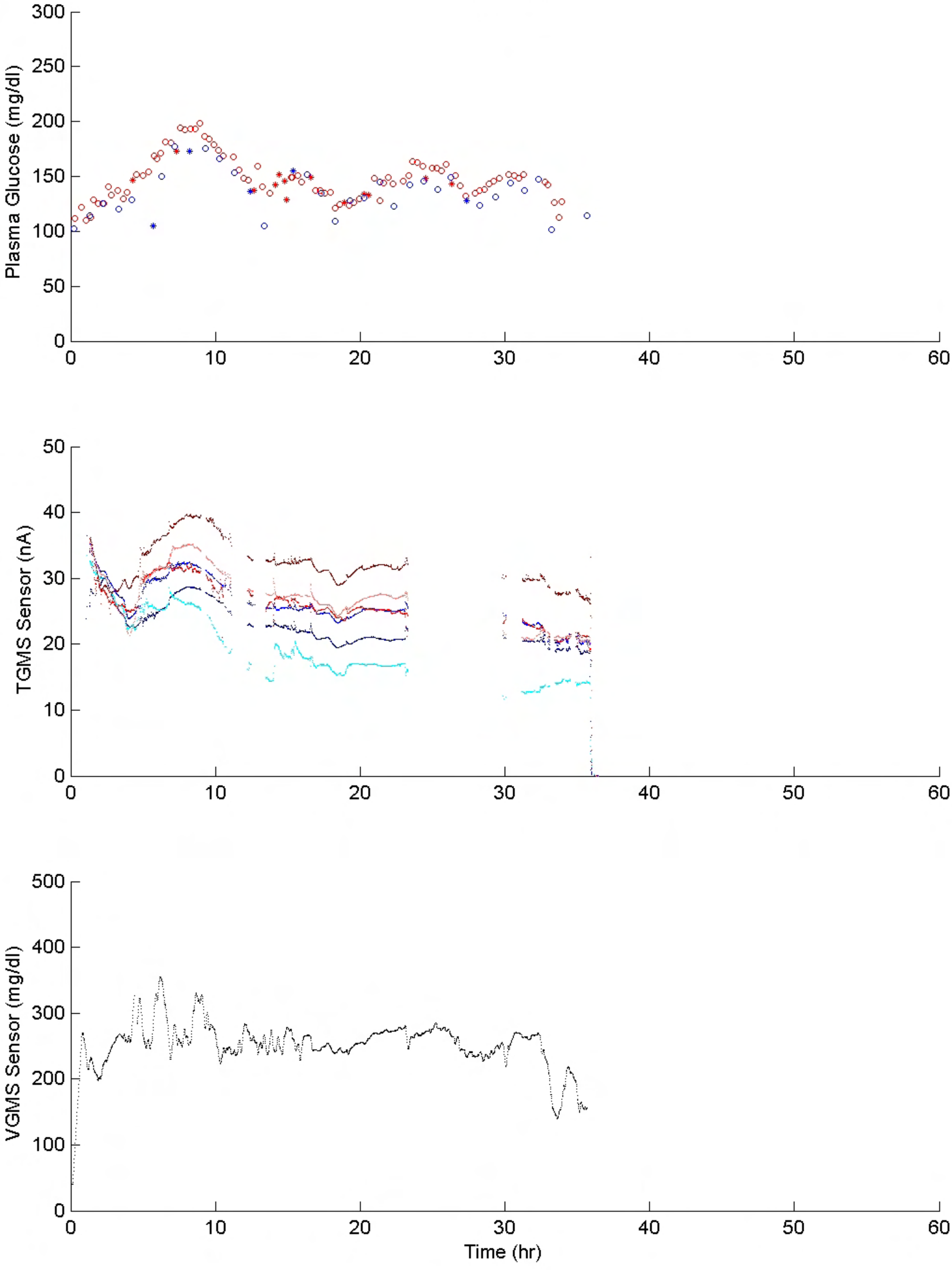
VGMS Sensor (mg/dl)

Time (hr)

Patient A3


Plasma Glucose (mg/dl)
300
250
200
150
100
50
0
0
10
20
30
40
50
60
TGMS Sensor (nA)
50
40
30
20
10
0
0
10
20
30
40
50
60
VGMS Sensor (mg/dl)
500
400
300
200
100
0
0
10
20
30
40
50
60
Time (hr)

Patient B3


Plasma Glucose (mg/dl)
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TGMS Sensor (nA)
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VGMS Sensor (mg/dl)
500
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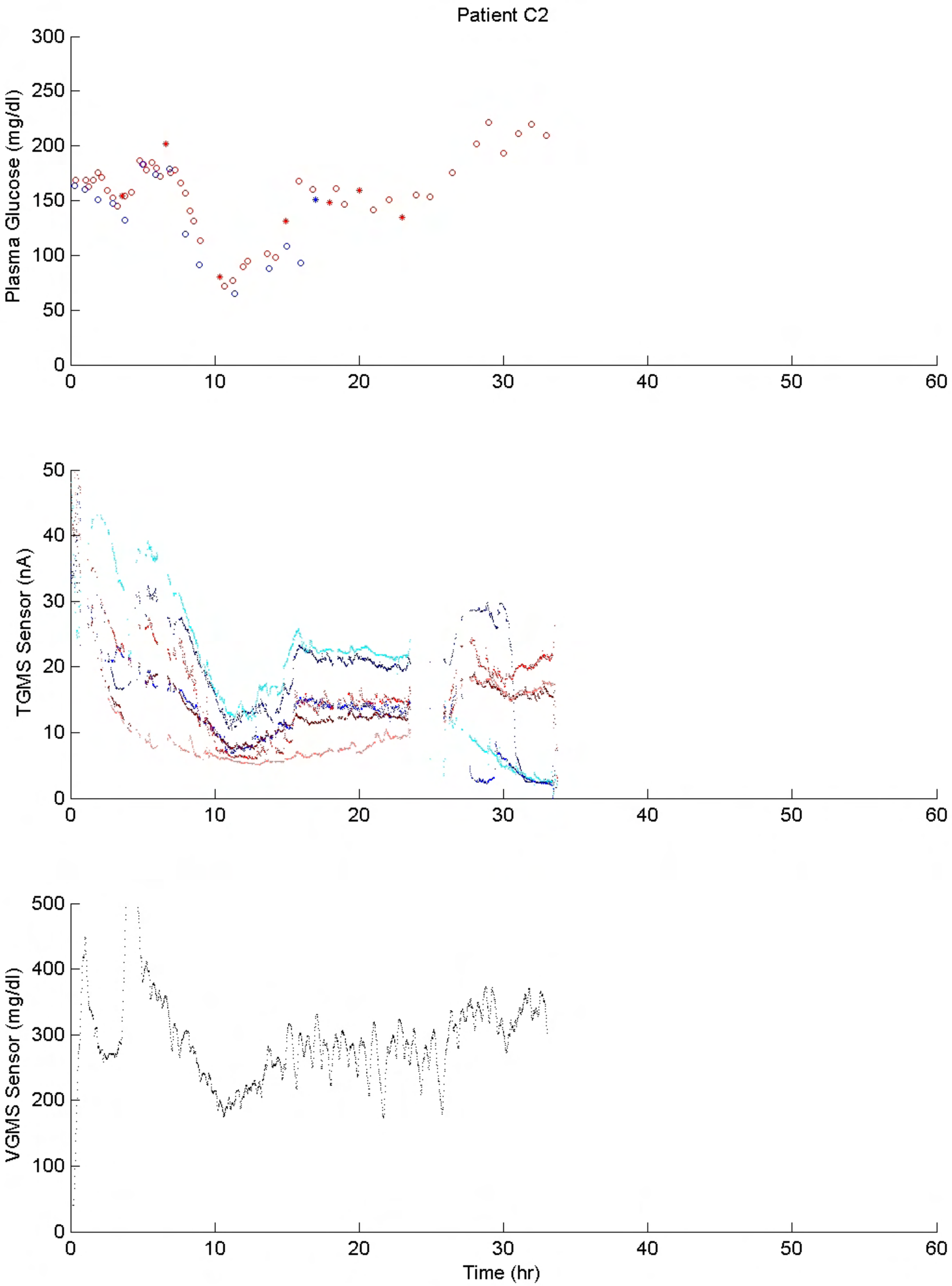
Time (hr)


Patient C2
Plasma Glucose (mg/dl)
300
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60
TGMS Sensor (nA)
50
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30
20
10
0
0
10
20
30
40
50
60
VGMS Sensor (mg/dl)
500
400
300
200
100
0
0
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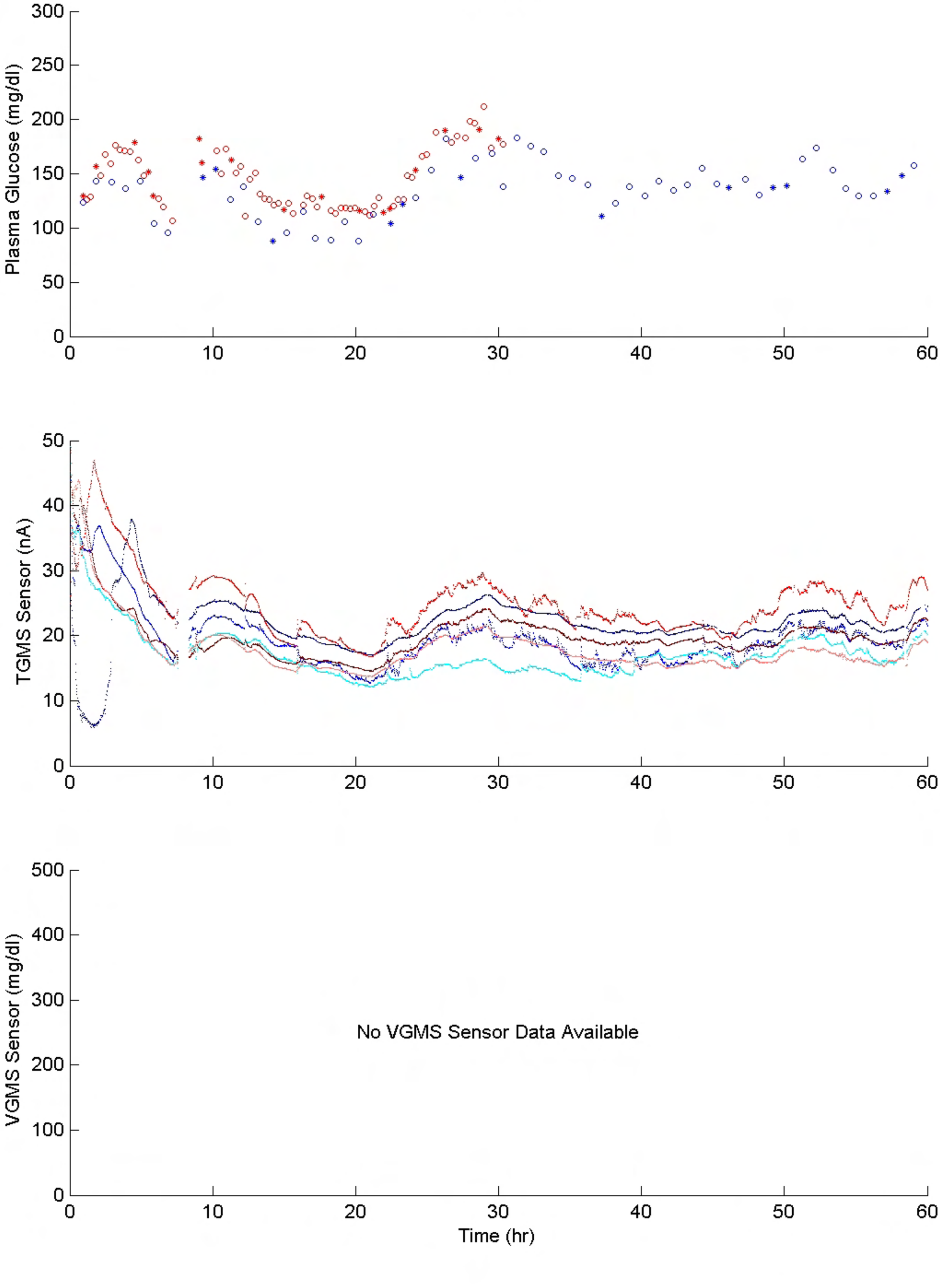
30
40
50
60
Time (hr)

Patient C3


Plasma Glucose (mg/dl)
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50
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TGMS Sensor (nA)
50
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30
20
10
0
0
10
20
30
40
50
60
VGMS Sensor (mg/dl)
500
400
300
200
100
0
No VGMS Sensor Data Available
0
10
20
30
40
50
60
Time (hr)

Patient D3

Plasma Glucose (mg/dl)

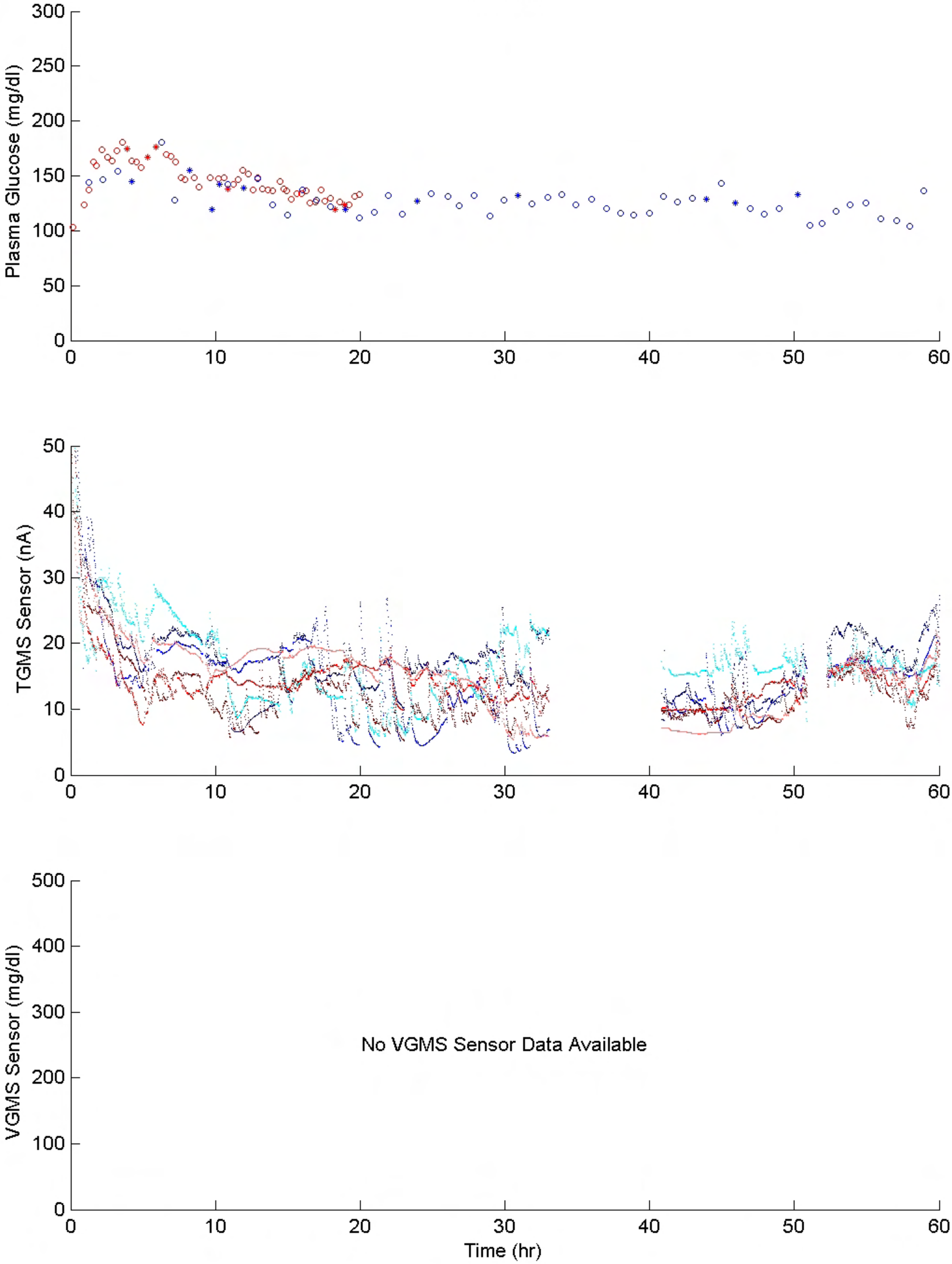
TGMS Sensor (nA)

VGMS Sensor (mg/dl)

No VGMS Sensor Data Available

Time (hr)

Patient E3


Plasma Glucose (mg/dl)
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TGMS Sensor (nA)
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VGMS Sensor (mg/dl)
500
400
300
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0
No VGMS Sensor Data Available
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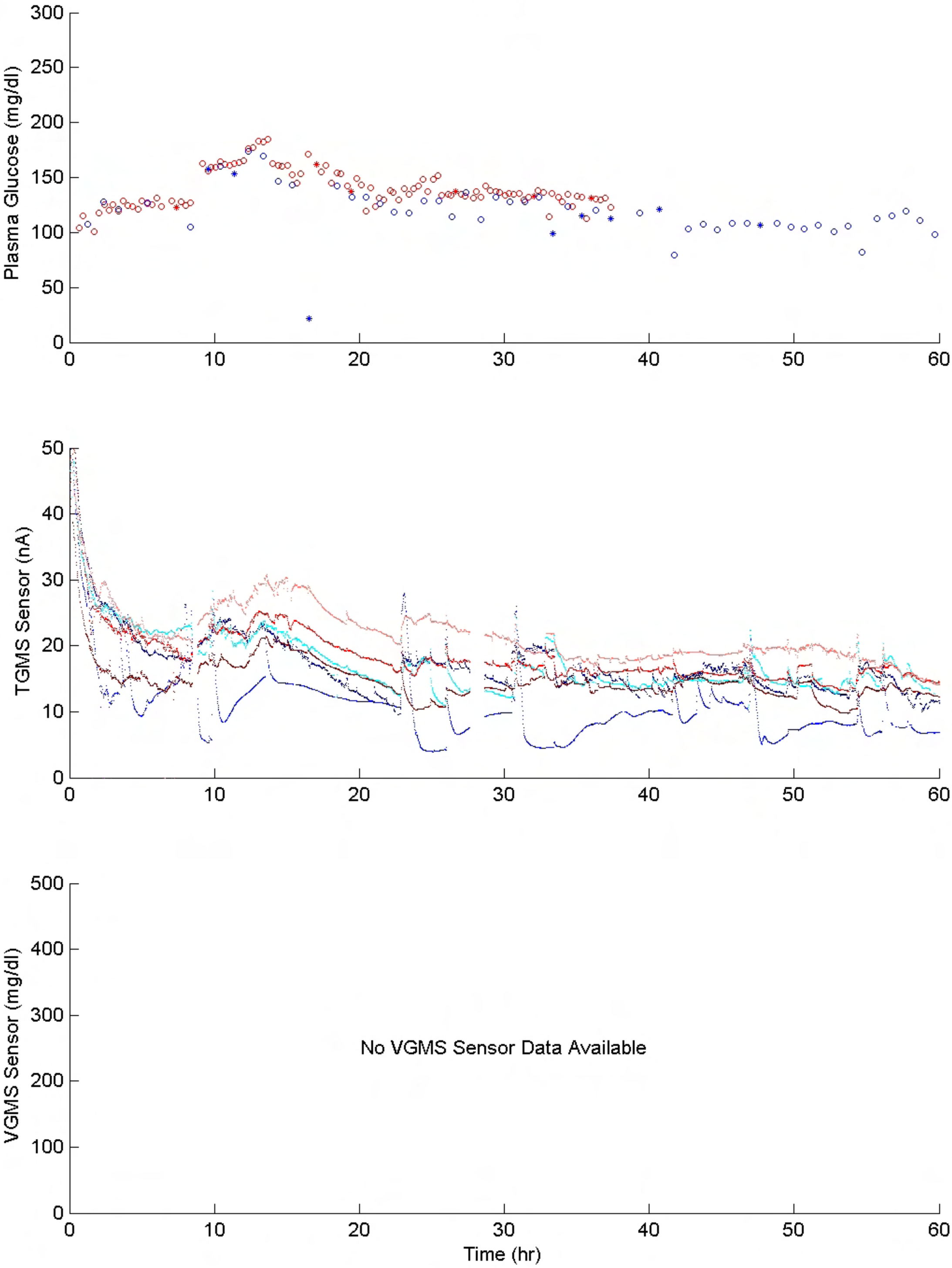
Time (hr)

Patient F3


Plasma Glucose (mg/dl)
300
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TGMS Sensor (nA)
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VGMS Sensor (mg/dl)
500
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No VGMS Sensor Data Available
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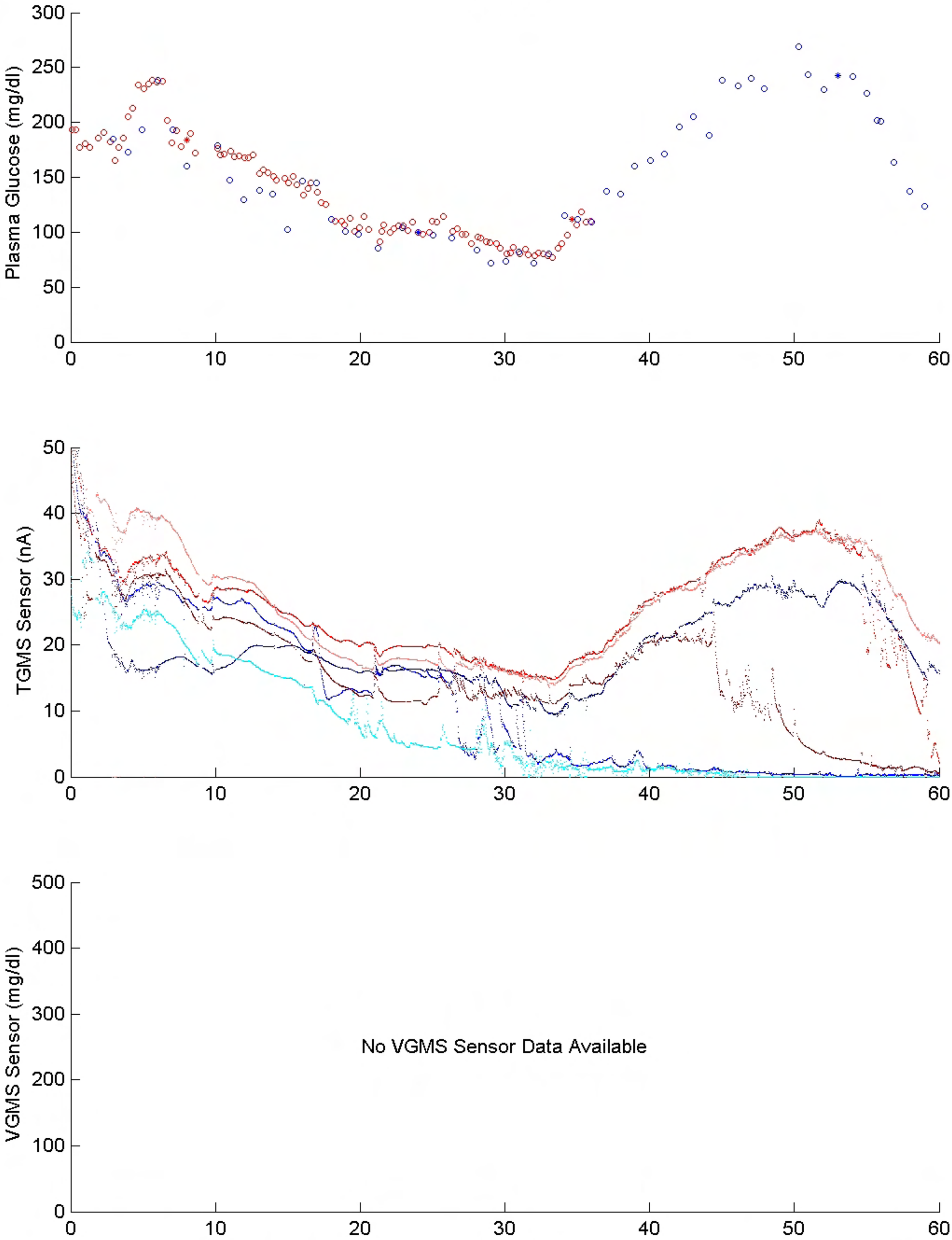
Time (hr)

Patient D2


Plasma Glucose (mg/dl)
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TGMS Sensor (nA)
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VGMS Sensor (mg/dl)
500
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300
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100
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No VGMS Sensor Data Available
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50
60
Time (hr)

Appendix 2: Data Analysis Plan

Plan for Data Analysis

The correlation between reference and sensor glucose readings will be calculated using the Pearson Product Moment Correlation - it will be designated by the letter R. The Mean Absolute Deviation (MAD) is a measure of the average difference between reference and sensor glucose readings. The formulations for these two statistics are:

$$R = \frac{\sum xy - \frac{1}{n}\sum x \sum y}{\sqrt{\left(\sum x^2 - \frac{1}{n}\left(\sum x\right)^2\right)\left(\sum y^2 - \frac{1}{n}\left(\sum y\right)^2\right)}} \text{ and } MAD = 100\frac{1}{n}\sum \frac{|x-y|}{x}$$

where *x* and *y* are paired values of the reference and sensor glucose readings, respectively, and *n* is the number of paired values. Because reference values have been obtained from several sampling sites (*i.e.*, arterial, venous and capillary), these statistics will be computed for each set separately (*e.g.*, correlation of sensor values to reference arterial blood).

Sensor Accuracy and Run-in Time

Statistics: R, MAD

Endpoints: R > 0.90 and MAD < 20% will indicate adequate tracking of reference glucose measurements by the sensor. Significant differences ($p < 0.05$) in R and MAD statistics obtained under different run-in times will be reported.

Expected Outcome: Medtronic MiniMed scientists working with the ISF sensor (TGMS, Telemetered Glucose Monitoring System, Medtronic MiniMed, Northridge, CA) report a run-in time of 2-3 hours. Previous clinical trials reported an average MAD of 30% and 18.5%; and an average R of 0.96 (range of R from individual sensors was 0.72-1.00) for the TGMS.

Procedure: Run-in times from 0 to 6 hours will be investigated in 1-hour increments. Sensor data prior to the chosen run-in time will be excluded. The electrical current data from the glucose sensors will be filtered. A linear transformation (scale and offset values to map the filtered sensor current values to sensor glucose readings) will be computed to minimize the squared error between paired reference and sensor glucose readings. R and MAD statistics will be computed for each sensor for each run-in time. Student t tests[1] will be used to determine if there is a significant improvement in R and MAD statistics for different run-in times.

Comments: In addition to the analysis described above, student t test will be used to determine if significant differences ($p < 0.05$) exist for the R and MAD statistics between the two sites (*e.g.*, abdomen and upper arm) for the TGMS sensors.

Sensor Accuracy and Recalibration Frequency

Statistics: R, MAD

Endpoints: R > 0.90 and MAD < 20% will indicate adequate tracking of reference glucose measurements by the sensor. Significant differences ($p < 0.05$) in R and MAD statistics obtained under different recalibration frequencies will be reported.

Expected Outcome: A TGMS sensor is expected to experience signal degradation through its lifetime and several one-point recalibrations will be required to provide adequate tracking to reference glucose readings.

Procedure: An appropriate run-in time for each technology will be identified (see *Sensor Accuracy and Run-in Time* above). Sensor data collected during the run-in time will not be used in this analysis (time period when sensor is equilibrating with environment). An initial two-point calibration will be performed using reference arterial glucose readings to obtain linear equation coefficients (scale and offset) that transform the sensor output current to a glucose value. One-

[1] or equivalent non-parametric test

point recalibration will be performed at various frequencies (*e.g.*, 1 recalibration per 60, 40, 30, 24, 20, 16, 12, 10, 8, 6, 4, 2 hours). For each sensor and each recalibration frequency, the R and MAD statistics will be calculated and recorded. The percentage of TGMS sensors that achieved the endpoints for each recalibration frequency will be reported. Student t tests will be used to determine if there is significant improvement in R and MAD statistics for different recalibration frequencies.

Combination of Sensor Measurements
Statistics: R, MAD
Endpoints: Identify signal processing techniques that lead to significant improvement ($p < 0.05$ as measured by student t-test or Wilcoxon test) in R and MAD statistics for TGMS1 combined-sensor glucose readings.
Expected Outcome: The combination of multiple TGMS sensor signals will improve the accuracy of the glucose measurement.
Procedure: For each experiment, every possible combination of grouping using 2 to 6 TGMS sensors will be explored (including using sensors from different sites). Signals will be averaged with and without employing a Zero-mean, Mean Absolute Deviation (ZMAD) statistic[2] or equivalent to exclude outlying signals.
An appropriate run-in time for each technology will be identified (see *Sensor Accuracy and Run-in Time* above). Sensor data collected during the run-in time will not be used in this analysis (time period when sensor is equilibrating with environment). An initial two-point calibration will be performed using reference arterial glucose readings to obtain linear equation coefficients (scale and offset) that transform the sensor output current to a glucose value. One-point recalibration will be performed at various frequencies (*e.g.*, 1 recalibration per 60, 40, 30, 24, 20, 16, 12, 10, 8, 6, 4, 2 hours). For each sensor combination and each recalibration frequency, the R and MAD statistics will be calculated and recorded. For each sensor combination, student t tests will be used to determine if there is significant improvement in R and MAD statistics for the same recalibration frequency when compared to single sensor results (as well other sensor combinations).
Comments: The procedure is similar to *Sensor Accuracy and Recalibration Frequency* analysis (see above) so results can be compared. Sensor combinations include:

- 2 sensors, same site, without ZMAD exclusion statistic
- 2 sensors, different sites, without ZMAD exclusion statistic
- 3 sensors, same site, without ZMAD exclusion statistic
- 3 sensors, different sites, without ZMAD exclusion statistic
- 3 sensors, same site, with ZMAD exclusion statistic
- 3 sensors, different sites, with ZMAD exclusion statistic
- 4 sensors, different sites, without ZMAD exclusion statistic
- 4 sensors, different sites, with ZMAD exclusion statistic
- 5 sensors, different sites, without ZMAD exclusion statistic
- 5 sensors, different sites, with ZMAD exclusion statistic
- 6 sensors, different sites, without ZMAD exclusion statistic
- 6 sensors, different sites, with ZMAD exclusion statistic

Long-Term Sensor Model
Statistics: R, MAD

[2] for more information on the ZMAD statistic, please see Ward WK, Casey HM, Quinn MJ, Federiuk IF, Wood MD: A Fully Implantable Subcutaneous Glucose Sensor Array: Enhanced Accuracy from Multiple Sensing Units and a Median-Based Algorithm. Diabetes Technology & Therapeutics, 1 December 2003, 5(6), 943-952.

Endpoints: Develop a mathematical model of typical sensor behavior for the TGMS. Determine if this model can be employed to reduce the need for frequent recalibration and identify dysfunctional sensors.
Expected Outcome: The recalibration frequency of the TGMS will be reduced (while maintaining accuracy) if the sensor drift is predictable.
Procedure: Data from properly functioning sensors will be identified for analysis (including data from replacement sensors). For each sensor, sensitivity versus time will be calculated using the sensor current values and reference arterial glucose measurements. A mathematical expression (*i.e.*, long-term sensor model) describing the time-course of sensor sensitivity will be developed.
Sensor Recalibration The long-term sensor model will be used to modify the linear equation coefficients (scale and offset). R and MAD statistics will be generated and compared to results from *Sensor Accuracy and Recalibration Frequency*.
Failure Detection A failure detection algorithm will be developed using the long-term sensor model. The ability of the algorithm to identify malfunctioning sensors will be tested using actual data collected from malfunctioning sensors. Sensitivity and specificity of the detection algorithm will be reported.

Correlation of Supplemental Clinical Measurements
Statistics: R
Endpoints: $R > 0.80$
Expected Outcome: The sensor output currents of the TGMS technology is highly specific to glucose but certain blood chemistries may affect sensor sensitivity. These possible correlations will be investigated.
Procedure: Sensor current values will be paired with reference clinical measurements. The R statistic will be calculated for these paired measurements. $R > 0.80$ will indicate a significant relationship between the sensor output and clinical measurement.

Appendix 3: 2006 ASA Abstracts

1. Hipszer B, Furlong KJ, Lessin JB, Grunwald Z, Joseph JI. Continuous Glucose Monitoring in the Perioperative Period. Abstract, ASA Annual Meeting of the American Society of Anesthesiology, October 2006, Chicago, IL.
2. Hipszer B, Joseph JI. Lag Associated with Interstitial Glucose Sensors used in a Diabetic Surgical Patient. Abstract, Annual Meeting of the American Society of Anesthesiology, October 2006, Chicago, IL.

Title: Continuous Glucose Monitoring in the Perioperative Period

Brian R Hipszer, MS, Kevin J Furlong, DO, Jennifer B Lessin, RN, Zvi Grunwald, MD, Jeffrey I Joseph, DO

Summary
The performance of two glucose sensing technologies was evaluated in a diabetic surgical patient. The interstitial fluid sensors had a higher correlation (R=0.906) than the vascular sensor (R=0.761).

Background
Continuous glucose monitoring has the potential to improve glycemic control in hospitalized patients with diabetes or stress hyperglycemia. Real-time glucose information will allow aggressive titration of insulin and glucose to achieve and maintain euglycemia, decrease staff workload, and alleviate the fear of hypoglycemia.

Materials and Methods
The performance of a modified Guardian RT System (SC sensor) and Vascular Glucose Monitoring System (IV sensor) was evaluated over 60 hours in the perioperative period. Six SC sensors and one IV sensor were inserted in a surgical patient with type 2 diabetes. Each SC sensor was inserted into the subcutaneous tissue and provided a measurement of the interstitial fluid glucose concentration every minute. The IV sensor was inserted through a central venous catheter and provided a measurement of the blood glucose concentration every minute.

All sensors were inserted preoperatively using an aseptic technique. Three SC sensors where inserted through the skin in the upper right chest wall region (sensors 1-3). An additional three SC sensors were inserted in the right upper arm (sensors 4-6). The IV sensor was inserted through a right internal jugular vein central venous catheter so that the distal tip floated freely at the junction of the superior vena cava and right atrium. The patient experienced minimal discomfort during sensor insertions. Reference blood samples were obtained from a radial artery catheter every 20 minutes and assayed for the concentration of glucose using an OMNI 9 Blood Gas Analyzer (Roche Diagnostics).

Analysis was performed on a continuous 40-hour block of data that began 7 hours and 43 minutes after the sensors were inserted, starting in the post operative period. The Pearson correlation coefficient (R) between the reference and sensor measurements was calculated. Paired values were obtained by matching the closest sensor measurement in time with its corresponding reference measurement. The sensor data was not calibrated to reference measurements. The IV sensor data was based on an in-vitro calibration curve.

Results
The sensitivity of SC sensors drifted significantly in the first few hours after subcutaneous insertion (run-in time) whereas the IV sensor did not require a run-in period. In Figure 1, the reference glucose measurements are plotted with the output signals from SC sensors (upper panel) and the IV sensor (lower panel). R was 0.906 ±

0.014 (mean ± SD) for the SC sensors and 0.761 for the IV sensor.

Conclusions

The SC sensor measurements produced better correlation with reference arterial blood glucose measurements than those from the IV sensor. Whereas the SC sensor measures the hydrogen peroxide end-product of the glucose oxidase reaction, the IV sensor measures the amount of oxygen consumed by the reaction and is susceptible to sudden changes in a patient's oxygen levels. The performance of the IV sensor would improve with real-time recalibrations.

Acknowledgements

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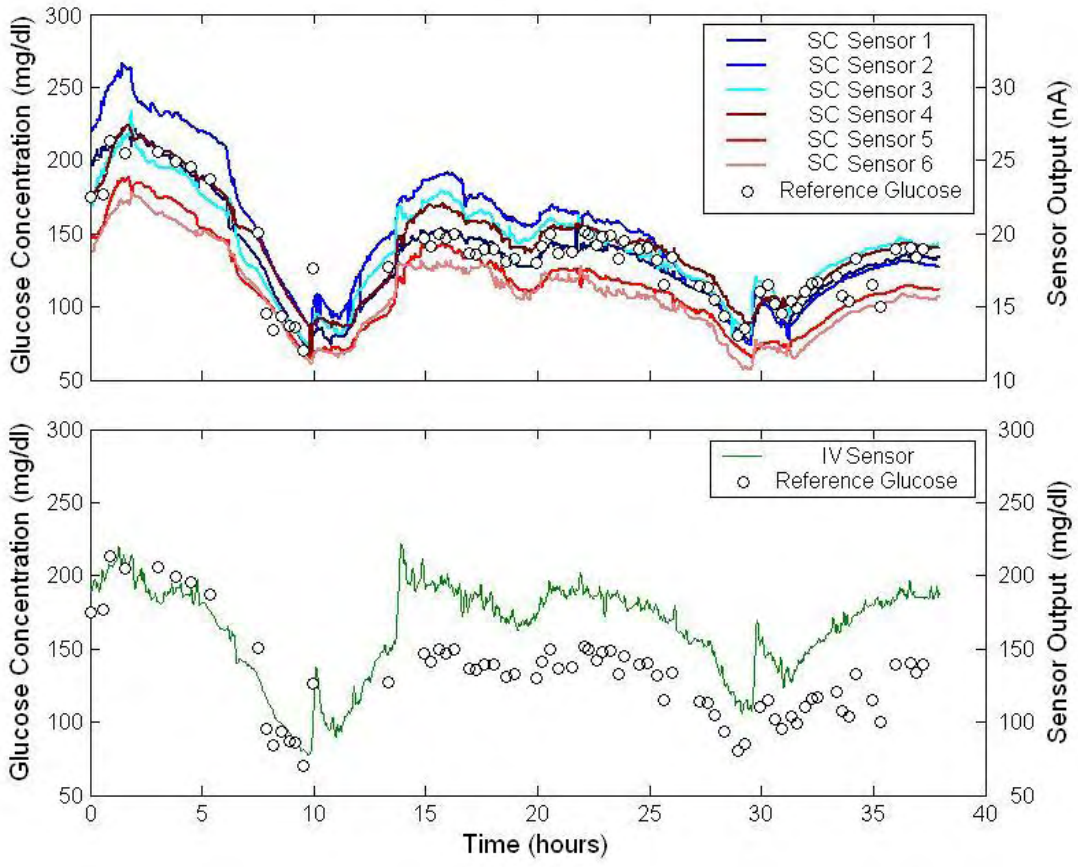
Figure 1: Measurements from the OMNI 9 (reference), SC sensors and IV sensor



Title: Lag Associated with Interstitial Glucose Sensors used in a Diabetic Surgical Patient

Brian R Hipszer, MS, Jeffrey I Joseph, DO

Summary
The performance of six interstitial fluid glucose sensors simultaneously inserted in the subcutaneous tissue of a diabetic patient undergoing major surgery was studied. On average, the interstitial fluid sensor measurements lagged the arterial plasma glucose measurements by 15 minutes.

Background
Continuous glucose monitoring has the potential to improve glycemic control in the hospital. Device characterization is important to understand the limitations of sensor technology.

Materials and Methods
Six investigational interstitial fluid (ISF) glucose sensors were simultaneously inserted in a patient with type 2 diabetes prior to surgery. The sensing portion of the ISF sensor was identical to the Guardian® RT Continuous Glucose Monitoring System commercialized by Medtronic Diabetes (Northridge, CA). Sensors were grouped in two arrays, one in the lateral right chest (sensors 1-3) and the other in the upper right arm (sensors 4-6). Sensor measurements were wirelessly transmitted to a laptop computer every minute for 60 hours. Reference glucose measurements were taken in duplicate every 20 minutes using arterial blood. Only duplicate reference measurements that differed by less than 10% were used in the subsequent analysis.

Analysis was performed on a continuous 40-hour block of data that began 7 hours and 43 minutes after the sensors were inserted and 4 hours and 4 minutes after the surgery was completed. The Pearson correlation coefficient (R) between the reference and sensor measurements was calculated. Since the frequency of measurement differed, paired values were obtained by matching the closest sensor measurement in time with its corresponding reference measurement. To determine the time lag between the reference and sensor measurements, the sensor measurements were shifted in time and R was calculated for each shift. The shift that produced the largest value for R was determined to be the time lag between the reference and sensor measurements.

Results
On average, the sensor measurements lagged the reference measurements by 15±6.5 minutes (mean± SD). Using an unpaired Student's t-test to compare the lags from the two sensor arrays, it is improbable that the lags from the arm array came from the same sample population as those from the chest array ($p<0.05$).

Conclusions
The time lag between ISF glucose sensor measurements and reference blood glucose

measurements is the sum of the physiological and instrumental lags. Previous studies in healthy outpatient diabetic subjects observed lags between 0-10 minutes[1-3]. The 1-minute sensor measurement used in the current analysis provided far greater time resolution. Although current analysis did not use any filtering of the sensor measurements, a commercial ISF sensor would most likely use a filter to suppress noise. Real-time filtering, however, can add further delays.

References

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Table 1: The maximum correlation (R) achieved by shifting the sensor measurements in time and the lag between the reference and sensor measurements

	Sensor 1	**Sensor 2**	**Sensor 3**	**Sensor 4**	**Sensor 5**	**Sensor 6**
R_{max}	0.937	0.915	0.900	0.928	0.919	0.914
Lag (min)	11	14	5	20	23	17

Appendix 4: Research Personnel

Investigators:

Name	Role	Pay Received For This Research
Jeffrey Joseph, DO	Principal Investigator	Yes
Brian Hipszer, MS	Co-Investigator	Yes
David Gratch, DO	Co-Investigator	No
David Maguire, MD	Co-Investigator	No
James Heitz, MD	Co-Investigator	No
Charles Yeo, MD	Co-Investigator	No
Zvi Grunwald, MD	Co-Investigator	No
Barry Goldstein, MD, PhD	Medical Monitor	Yes

Data Collection Personnel:

Name	Role	Pay Received For This Research
Adrianne Moore	Research Nurse	Yes
Amy Callahan	Research Nurse	Yes
Ann Liotino	Research Nurse	Yes
Anne Marlay	Research Nurse	Yes
Ashley Benedict	Research Nurse	Yes
Bonnie Grady	Research Nurse	Yes
Brooke Redeyoff	Research Nurse	Yes
Carleo Naluan	Research Nurse	Yes
Carrie Christiansen	Research Nurse	Yes
Cheryl Starrett	Research Nurse	Yes
Cindy Trappler	Research Nurse	Yes
Dawn Fisher	Research Nurse	Yes
Dawn Gillespie	Research Nurse	Yes
Dorothy Lang	Research Nurse	Yes
Dyllan Siemann	Research Nurse	Yes
Eileen Donnelly	Research Nurse	Yes
Elise Dorr-Dorynek	Research Nurse	Yes
Jason McConomy	Research Nurse	Yes
Jennifer Lessin	Research Nurse	Yes
Jennifer Soares	Research Nurse	Yes
John Furlong	Research Nurse	Yes
Julia Snyder	Research Nurse	Yes
Kate Ashburn	Research Nurse	Yes
Kate Passey	Research Nurse	Yes
Kathleen O'Malley	Research Nurse	No
Kerin Perry	Research Nurse	Yes
Larissa Lightstone	Research Nurse	Yes
Lisa Wus	Research Nurse	Yes
Neil Seligman	Research Nurse	Yes
Patti McGovern	Research Nurse	Yes

Sean McShane	Research Nurse	Yes
Teresa Campo	Research Nurse	Yes
Paul Didomenico	Technician	Yes
Carin Kozlowski	Technician	Yes
Michael Picone	Technician	Yes
Matthew Muffly	Technician	Yes
Patrick Shum	Technician	Yes
Garry Powell	Technician	Yes
Amanda Furlong	Technician	Yes
Jonathan Tannebaum	Technician	Yes
Cheryl Starrett	Technician	Yes
Waleed Shah	Technician	Yes
Joanne Vesci	Technician	No